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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/125,887	10/05/98	BOON-FALLEUR	T	EX96002-US

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EXAMINER	
BECKERLEG, A.	
ART UNIT	**PAPER NUMBER**
1632	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

File

Office Action Summary	Application No. 09/125,887	Applicant(s) Boon-Falleur et al.
	Examiner Anne Marie S. Beckerleg	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *20-40* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *20-40* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: *France 96/03207 3/14/96*.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

This application has missing parts. The specification discloses Figures 1-5 and Tables 1-4. While Tables 1-4 are present in the application, Figures 1-5 are missing. Submission of Figures 1-5 is required to complete the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for cells infected *in vitro* with a replication defective recombinant adenovirus encoding a tumor specific antigen and methods of preparing cytotoxic T cells specific for a tumor antigen *in vitro* comprising contacting cytotoxic T cell precursors with professional antigen presenting cells infected with said adenovirus, does not reasonably provide enablement for pharmaceutical compositions of said adenoviruses, or for methods of preparing cytotoxic T cells *in vivo* using said adenoviruses or cells infected with said adenoviruses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to use the invention commensurate in scope with these claims. It is noted that the claims 35 and 36 read on *in vivo* cell compositions.

The specification discloses replication defective recombinant adenoviruses encoding a tumor associated antigen or a fragment of a melanoma associated antigen which includes an MHC class I binding cytotoxic T cell epitope. The specification clearly discloses that the purpose of the instant invention is the therapy of cancer, specifically melanoma, and discloses that the intended use of the adenoviral vectors and methods of stimulating cytotoxic T cells is for *in vivo* cancer therapy.

The specification does not provide an enabling disclosure for stimulating cytotoxic T cell precursors *in vitro or in vivo* with any and all cells infected with a replication defective recombinant adenovirus encoding any tumor associated antigen or antigenic peptide from any tumor associated antigen. Activation of naive T cells requires the engagement of multiple receptors on the naive T cell. In addition to signaling through the T cell receptor following recognition and binding of the TCR to an appropriate peptide/MHC class I complex on an antigen presenting cell, T cell activation needs a "second signal", which can be provided by cytokines such as IL-2 binding to the IL-2R on the T cell , or by the binding of B7 on the APC with CD28 on the T cell. In the absence of a second signal, the T cell becomes tolerized rather than activated (Gilbert et al. (1994) J. Exp. Med., Vol. 179, page 249 abstract, Fuchs et al. (1992) Science, Vol. 258, page 1156, abstract). Cytokines such as IL-2 can be provided to the naive CD8+ T cell by helper CD4+ T cells which are activated by the binding of their TCR with peptide MHC class II

complexes on professional antigen presenting cells. Professional antigen presenting cells, such as dendritic cells and macrophages, can be differentiated from other antigen presenting cells by the expression of B7 and MHC class II. Thus, in the absence of exogenous administration of a cytokine such as IL-2, stimulation of naive T cells requires the interaction of the T cell with a professional antigen presenting cells such as a dendritic cell or macrophage. Therefore, based on the state of the art of naive T cell stimulation at the time of filing and the breadth of the claims, the skilled artisan would have considered it unpredictable to stimulate T cell precursors *in vitro* or *in vivo* with non-antigen presenting cells infected with a recombinant adenovirus of the instant invention.

The specification does not provide an enabling disclosure for preparing tumor antigen specific cytotoxic T cells *in vivo* by administering a recombinant adenovirus encoding any and all tumor antigens by any and all means and routes of delivery to any patient. The specification presents several *in vitro* experiments demonstrating that antigen presenting cells infected with recombinant adenoviruses encoding a fragment of MAGE-1 that includes an MHC class I epitope are capable of stimulating activated MAGE-1 specific cytotoxic T cell clones. As the T cells in these experiments are not naive T cell precursors, the relevance of these data are difficult to evaluate. As discussed above, the art teaches that the threshold for stimulation of naive versus activated T cells is quite different and requires different levels of costimulation. Further, in regards to the correlation between *in vitro* and *in vivo* data, Bachmann et al. stresses that caution should

be used to interpret *in vitro* CTL data without *in vivo* confirmation (Bachmann, M.F. et al (1994),Current Opin. Immunol., Vol.6, abstract and page 323 col.2 conclusion).

The specification does provide *in vivo* examples of the instant invention which consist of the administration of an adenovirus encoding the P1A tumor antigen by various routes of administration to mice. It is noted that P1A is not a melanoma antigen. The examples disclose that splenic T cells are isolated from the mice post adenoviral exposure and re-stimulated *in vitro* using L1210 leukemia cells transfected with the P1A gene. Table 4 show that the majority of mice which were injected in single locations, intraperitoneal (i.p.), intranasal, intratracheal, or subcutaneous (subq.) did not produce splenic T cells that demonstrated P1A cytotoxic activity after *in vitro* stimulation. On the other hand, Table 3 shows that 3/4 mice injected in two locations, i.p. and subq. did result in splenic T cells with P1A cytotoxicity. However, Table 3 also demonstrates that the splenic T cell cultures were equally stimulated by the L1210 cells alone in the absence of P1A, and that P1A specific lysis could only be observed with the addition of cold L1210A- targets. Thus, it appears that the *in vitro* stimulation step with the L1210A+ cells was capable of stimulating cytotoxic T cell precursors against non P1A antigens presented by the L1210 cells. Therefore, it is unclear whether the cytotoxic activity observed is the result of stimulation of T cell precursors *in vivo* by adenovirally infected APC or by stimulation of the splenic T cells *in vitro* by the L1210A+ cells.

It is further noted that the specification does not provide any data correlating the observed *in vitro* cytotoxic T cell activity with the activity of the T cells *in vivo* against cells expressing the

tumor antigen. As discussed above, the specification clearly discloses that the purpose of preparing tumor antigen specific cytotoxic T cells in the patient is for the treatment of tumors which express those antigens. The specification does not provide guidance for the level of tumor antigen specific cytotoxic T cell stimulation necessary to achieve any therapeutic response on a tumor encoding said antigen or provide sufficient guidance for the dosage and routes of administration of recombinant replication deficient adenovirus encoding a tumor antigen to patients including humans wherein T cell precursors are stimulated such that an antitumor therapeutic effect is observed. At the time of filing, the art teaches that *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are

great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins. In addition, cancer immunotherapy using tumor antigens is further complicated by the fact that in order for the tumor antigen specific T cells to be effective against the tumor, the tumor must be able to express recognizable levels of peptide/MHC class I complexes derived from tumor antigen. At the time of filing, the art teaches that tumors evade immune responses by a variety of mechanisms including down-regulation of TAP and MHC-encoded proteasome components, loss of antigenic epitopes by either lack of expression or mutations, loss of functional β_2m expression , and loss of particular MHC class I alleles (Restifo et al (1993) J. Immunother., Vol. 14, page 183, col 1, lines 8-14, and page 184, col. 2). The loss or mutation of any of these molecules would prevent from being recognized by the tumor specific cytotoxic T cells. Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following administration of adenoviral vectors and the mechanisms used by tumor to evade immune responses, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of tumor antigen to professional APCs *in vivo*, the lack of correlation between the specification's working examples and the production of tumor specific cytotoxic T

cells *in vivo*, and the breadth of the claims, it would have required undue experimentation to practice the scope of the instant invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The applicant claims methods of preparing cytotoxic T cells either by contacting T cell precursors with cells infected with a recombinant adenovirus or by administering a recombinant adenovirus to a patient. It is noted that the claims read on the preparation of cytotoxic T cells *in vivo*. In the *in vivo* context, the term "preparing" is confusing as it suggests the preparation of a specific isolated substance, in the instant case cytotoxic T cells, whereas the claims do not include methods steps for isolating the stimulated cytotoxic T cells from the mammal. Therefore, it is unclear in claims 38 and 40 whether the applicant intends to claim a method of preparing cytotoxic T cells or a method of preparing a patient containing tumor specific cytotoxic T cells, and in claims 37 and 39 whether the cells are infected *ex vivo* and then administered to the patient, or whether the cells are infected directly *in vivo*.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-23, 29 and 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhai et al. (1995) Proc. Am. Assoc. Canc. Res., Vol. 36, page 491, abstract 2927. The applicant claims a replication defective recombinant adenovirus comprising a nucleic acid encoding a tumor-specific antigen. The applicant further claims wherein said adenovirus is human serotype Ad2, and said antigen wherein the tumor is a melanoma. In addition the applicant claims a composition of cells infected with said adenovirus, and said composition wherein the cells are antigen presenting cells. It is noted that although claim 23 recites that the nucleic acid encodes a fragment of an antigen specific to a human melanoma, the claim reads broadly as comprising any sequence which encodes said fragment. Thus, the claim reads on a full length gene which encodes a melanoma specific antigen.

Zhai et al. teaches replication defective recombinant adenoviruses of human serotype Ad2 which encode the melanoma specific antigens MART-1 or gp100. Zhai et al. further teaches the infection of HLA-A2+ cells with said adenoviruses (Zhai et al., supra, abstract). The HLA-A2+ cells are clearly antigen presenting cells as they express the class I molecule HLA-A2 and can be

recognized and lysed by antigen specific CTL (Zhai et al., supra, abstract). Thus, by teaching all the limitations of the claims, Zhai et al. anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhai et al. (1995) Proc. Am. Assoc. Canc. Res., Vol. 36, page 491, abstract 2927 in view of U.S. Patent No. 5,891,715 (Haddada et al.) 6/6/99, 102 (e) date: 11/29/95 . The applicant claims a replication defective canine adenovirus which encodes a tumor specific antigen. Zhai et al. teaches replication defective recombinant adenoviruses of human serotype Ad2 which encode the melanoma specific antigens MART-1 or gp100 (Zhai et al., supra, abstract). Zhai et al. differs from the instant invention in that it does not teach a canine adenovirus. U.S. Patent No. 5, 891,715, hereafter referred to as Haddada et al., teaches replication defective recombinant canine adenoviruses that encode any antigenic gene of interest (Haddada et al., column 10, claim 5, and column 4, lines 11-14). Haddada et al. further provides motivation for using canine adenoviruses rather than human adenoviruses by teaching that canine adenoviruses are advantageous to human

adenoviruses as they are incapable of propagating in human cells and cannot be trans-complemented by non-recombinant human adenoviruses (Haddada et al., column 1, lines 59-67, and column 2, lines 1-9). Therefore, based on the motivation to use canine adenoviruses rather than human adenoviruses provided by Haddada et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the canine adenovirus taught by Haddada et al. for the human adenovirus taught by Zhai et al.. Further, the skilled artisan would have had a reasonable expectation of success in making a canine adenovirus encoding the MART-1 or gp100 tumor antigens based on the teachings provided by Haddada et al. and Zhai et al. using well-known techniques in molecular biology.

Claims 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhai et al. (1995) Proc. Am. Assoc. Canc. Res., Vol. 36, page 491, abstract 2927 in view of Chen et al. (1996) J. Immunol., Vol. 156, 224-231. The applicant claims a replication defective recombinant adenovirus comprising a nucleic acid encoding a tumor-specific antigen wherein the adenovirus has a deletion in either E1 or E4 and wherein said nucleic acid is inserted into the D1 or E4 region.

Zhai et al. teaches replication defective recombinant adenoviruses of human serotype Ad2 which encode the melanoma specific antigens MART-1 or gp100 (Zhai et al., supra, abstract). Zhai et al. does not specifically teach where said antigenic sequences are inserted in the adenoviral genome, or teach whether E1 or E4 are deleted. Chen et al. supplements Zhai et al. by teaching a

replication defective recombinant adenovirus of human serotype Ad2 which encodes a model tumor antigen inserted into the E1 region wherein the adenovirus lacks both E1 and E4 sequences (Chen et al., supra, abstract, and page 225, figure 1). Chen et al. further provides motivation for using a replication defective recombinant adenovirus that lacks both E1 and E4 as the E1/E4-deleted adenovirus grows to much higher titers than non E1/E4 deleted virus (Chen et al., supra, abstract). Therefore, based on the motivation provided by Chen et al. to use adenoviruses with E1/E4 deletions for increased titers, it would have been *prima facie* obvious to the skilled artisan to substitute the replication defective adenovirus taught by Chen et al. for the adenovirus taught by Zhai et al. Further, based on the high level of skill in the art of molecular biology at the time of filing, the skilled artisan would have had reasonable expectation of success in generating a replication defective E1/E4 deleted recombinant adenovirus with a tumor specific antigen such as MART-1 or gp100 inserted into the E1 region.

Claims 24-28, 37 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toso et al. (1996) Cancer Res., Vol. 56, 16-20 in view of Zhai et al. (1995) Proc. Am. Assoc. Canc. Res., Vol. 36, page 491, abstract 2927 and Chen et al. (1996) J. Immunol., Vol. 156, 224-231. The applicant claims a replication defective recombinant adenovirus comprising a nucleic acid encoding a tumor-specific antigen selected from the group which includes MAGE-1, and methods of preparing cytotoxic T cells specific for a tumor antigen comprising contacting a cytotoxic T cell precursor with a population of cells infected with said adenovirus. It is noted that

the methods of claims 37 and 39 read on both *in vitro* and *in vivo* contact of cytotoxic T cell precursors with infected cell populations. Further, it is noted that while claims 25-28 read on nucleic acids encoding a peptide fragment of Mage-1 or Mage-3, the claims read broadly as comprising any sequence which encodes a peptide fragment of Mage-1 or Mage-3. Thus, the claim reads on a full length Mage -1 gene.

Toso et al. teaches a recombinant vaccinia virus which encodes the melanoma antigen MAGE-1 (Toso et al., supra, page 17). Toso et al. further teaches that cells infected with the recombinant vaccinia encoding MAGE-1 *in vitro* were capable of stimulating TILs derived from a breast cancer patient to proliferate and to lyse MAGE-1 expressing cells *in vitro* (Toso et al., supra, page 18, figures 2 and 3). Toso et al. differs from the instant invention as they use a recombinant vaccinia virus which encodes MAGE-1 rather than a replication defective adenovirus. Zhai et al. supplements Toso et al. by teaching the construction of replication defective recombinant adenoviruses of human serotype Ad2 which encode the melanoma specific antigens such as MART-1 or gp100 (Zhai et al., supra, abstract). Chen et al. provides motivation for substituting the recombinant adenoviruses taught by Zhai et al. for the recombinant vaccinia virus taught by Toso et al. by teaching that recombinant adenoviruses are preferred to other viral vectors such as vaccinia virus because the deficient adenoviruses cannot replicate, do not destroy the host cell, have prolonged periods of protein expression and are safe to use in humans (Chen et al., supra, page 229-230, bridging paragraph, and page 230 paragraph 2). Thus, based on the motivation provided by Chen et al. , it would have been *prima facie* obvious at the time of filing

for the skilled artisan to substitute the replication defective recombinant adenoviruses as taught by Zhai et al. for the recombinant vaccinia viruses taught by Toso et al. in order to stably express an encoded melanoma specific tumor antigen and stimulate T cells. Further, based on the high level of skill in molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in generating a recombinant adenovirus which encodes MAGE-1 rather than MART-1 using well known techniques in molecular biology and using said viral vector to infect antigen presenting cells according to the methodology taught by Toso et al..

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

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